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10/530,262	04/05/2005	Masahiko Koike	084437-0172	4696

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EXAMINER	
WELTER, RACHAEL E	

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1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,262	KOIKE ET AL.	
	Examiner	Art Unit	
	RACHAEL E. WELTER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 15-17 and 19-25 are pending. Claims 1-14 and 18 are cancelled.

Acknowledgment

Receipt of the Declaration and arguments/remarks filed on 3/12/10 is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 15-17, 19-21, 23, and 25 rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158; Published 5/10/2001) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by

Remington (*Remington: The Science and Practice of Pharmacy,* 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (http://www.rxlist.com/actos-drug.htm) is maintained.

Piper teaches a pharmaceutical formulation which includes a combination of metformin and at least one other antidiabetic agent (pg. 6, lines 28-31), which can be a thiazolidinedione (pg. 14, line 9), such as pioglitazone (pg. 15, line 20). As evidenced by Rx List, Takeda-Lilly-Actos (pg. 15, line 21) mentioned in Piper is a pioglitazone hydrochloride. Piper also teaches that the antidiabetic agent can be glyburide (pg. 8, lines 14-15). Furthermore, Piper teaches that the formulation has at least substantially equivalent efficacy in treating type 2 diabetes as compared to prior art antidiabetic formulations containing metformin, but with substantially reduced side effects (pg. 1, lines 10-14). In forming a low dose metformin hydrochloride and glyburide formulation, the granules are formed by wet granulation of a mixture of metformin and glyburide (pg. 23, lines 19-20). More specifically, Piper teaches that a dry mixture of croscarmellose sodium and glyburide were dispersed together followed by blending with the metformin hydrochloride/magnesium stearate in a high shear mixer with an aqueous povidone solution and dried. (pg. 26, lines 1-4). The dried granulation was reduced with a screening mill and mixed with microcrystalline cellulose using a tumble mixer (pg. 26, lines 8-10). Magnesium stearate was incorporated as a lubricant using a tumble mixer to produce the final compression blend (pg. 26, lines 10-12). The resultant blend was compressed into tablets and film-coated (pg. 26, lines 13-24). Because the granules are being formed from a mixture of metformin and glyburide and a high shear mixer is

used, the reference implies that the biguanide and pioglitazone are uniformly dispersed. Furthermore, Piper teaches that the glyburide has a particle distribution of a 25% undersize value not more than 6 um, a 50% undersize value (also known as the mass median particle size) 7 to 10 um, and a 75% undersize value not more than 23 um (pg. 23, lines 11-15). Piper further conducted a study with particle size data to achieve comparable bioavailability to Micronase (glyburide alone) from the combination product of glyburide and metformin (pg. 26, lines 24-29). According to Piper, the particle size values or particle distribution assured reproducibility of glyburide dissolution and bioavailability from metformin hydrochloride-glyburide tablets.

Piper does not explicitly teach a median particle size of biguanide (metformin) of 10-100 um or a ratio of median size biguanide particles to median size pioglitazone particles of 0.5 to 15.

However, according to Zhuang et al, a more uniform mixture is obtained by having a small particle size of each ingredient and a similar size of each ingredient (pg. 3, lines 4-5).

Therefore, given the teachings of Zhuang et al, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a similar biguanide median size to glyburide taught in Piper or its functional equivalent, pioglitzaone, resulting in a 1:1 ratio. One would have been motivated to do so in order to create a more consistent mixture during granulation because Zhuang et al suggest that similar sized ingredients make a more uniform mixture.

Furthermore, as evidenced by Remington and Piper, the particle size of a drug in an oral dosage form can affect its dissolution rates. According to Remington, higher dissolution rates may be achieved through the reduction of the particle size (pg. 675, column 1, "Effect of Particle Size On Dissolution"). Remington further teaches that in the case of cloramphenicol, formulations containing smaller particles (50-200 um) were absorbed faster than formulations containing larger particles (400-800 um). Moreover, as taught in Piper, the particle sizes of glyburide were based on achieving a desired bioavailability. Thus, it is well known in the art and it would be obvious to an artisan of ordinary skill to optimize and manipulate the particle sizes based on the desired dissolution rates and bioavailability of the drug.

Regarding claim 21 and the coefficient of variation of the pioglitazone, the examiner has no access to laboratory equipment and burden is on applicant to prove that the reference teaches otherwise. When the reference discloses all the limitations of a claim except a property or function and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, the examiner can shift the burden of proof to applicant as in *In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).*

Regarding claim 23, which is drawn to the dissolution rate of the formulation, this limitation is an intended use for the composition. Because it does not materially impact the structure of the composition itself, it is not given any patentable weight. Besides, the prior art teaches the obvious core structure of the solid formulation of metformin and pioglitazone, the formulation is capable of having the instantly claimed dissolution

characteristics when subjected to the Paddle Method depending on the amounts of drug, drug solubility, and median particle size. Further, one of ordinary skill in the art would have been motivated to alter the dissolution characteristics of a drug formulation depending on the needs of a particular patient population.

The rejection of claims 22 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158; Published 5/10/2001) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and Practice of Pharmacy,* 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (http://www.rxlist.com/actos-drug.htm) and further in view of *Remington (Remington's Pharmaceutical Sciences, 18th Edition, 1990, pg. 1639) and Kumar (US Patent No. 6,117,451; Published 9/12/2000) is maintained.

*Note: The Remington 18th Edition will be referred to as RPS in the body of this rejection.

The disclosures of Piper and Zhuang et al were discussed above.

Piper and Zhuang et al do not explicitly teach solid preparations having a hardness of 100-400 N.

RPS teaches that the resistance of a tablet to chipping, abrasion or breakage under conditions of storage, transportation, and handling before usage depends on its hardness (column 1, "Tablet Hardness", lines 1-3). According to RPS, a hardness of 4 kg, which corresponds to approximately 40 N, is considered to be a minimum for a satisfactory tablet.

Kumar teaches a metformin hydrochloride formulation capable of being directly compressed with specific excipients having desired hardness, disintegrating ability, and acceptable dissolution characteristics (column 4, lines 65-67--column 5, lines 1-5). According to Kumar, microcrystalline cellulose is an excipient that is highly compressible and produces hard, strong tablets at a low machine pressure (column 9, lines 18-20). Kumar further teaches that microcrystalline cellulose prevents chipping and capping of the metformin hydrochloride tablets (column 9, lines 20-21).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a tablet hardness of higher than 40 N. One would have been motivated to do so in order to make a satisfactory tablet that would be resistant to chipping, abrasion or breakage under certain conditions, as suggested by RPS.

Furthermore, as suggested by Kumar, it is known in the art to optimize and manipulate tablet hardness depending on a tablet's excipients and desired dissolution rate. Like Piper (see pg. 26, lines 8-10 of Piper), Kumar teaches microcrystalline cellulose as a preferred excipient and Kumar suggests a desired tablet hardness for metformin hydrochloride. Optimization of parameters is a routine practice that would be obvious to a person of ordinary skill in the art to employ and reasonably expect success. One would have been motivated to determine the optimal amount of each excipient in order to achieve the desired tablet hardness. See *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* & MPEP 2144.05. Burden is on the applicant to prove otherwise and show the criticality of the claimed hardness range.

Response to Arguments

Applicant's arguments and 1.132 Declaration filed 3/12/10 have been fully considered but they are not persuasive and insufficient respectively.

Applicant argues that the presently claimed preparations exhibit unexpected properties that make them suitable as an anti-diabetic combination drug. Applicant submitted a supplemental Rule 132 Declaration demonstrating these unexpected results. Applicant provides more evidence that equivalence can be achieved between pioglitazone in a combination drug and Actos (pioglitazone as the only active ingredient) in an in vitro dissolution test. However, bioequivalence of pioglitazone can only be achieved in a human body during clinical studies if the particles of the pioglitazone are micronized, specifically between 2-10 um as recited in instant claims 15 and 24. Applicant notes that such a discrepancy can be attributed to an unexpected in vivo drug interaction between the two active ingredients taking place in the human body, which is not only rare but also unpredictable to one of ordinary skill in the art. Applicant argues that the presently claimed invention provides a single-phase solid preparation, allowing the presently claimed preparation to be smaller in size, which at the same time allows both active ingredients to achieve bioequivalence. The Declaration additionally shows that the micronization of the pioglitazone particles did not significantly affect the uniformity of either of the active ingredients, contrary to the suggestion in the outstanding Office Action that one of ordinary skill in the art would have micronized pioglitazone for the purpose of increasing uniformity. Applicant further presents Exhibit A, which provides evidence that the glyburide of Piper shows a higher bioavailability

than a single agent of glyburide in Micronase. As such, Exhibit A clearly demonstrates that without micronization as presently claimed, bioequivalence of glyburide is not established. Thus, applicant argues that no combination of the cited references, Piper and/or Zhuang teaches or suggests that the lack of bioequivalence encountered when these drugs are combined could be overcome by a preparation featuring the selected combination of features recited in independent claims 15 and 24.

However, applicant's Rule 132 Declaration is insufficient to overcome the rejection of the claims as set forth in the last Office action because:

It is the position of the examiner that applicant's results would be expected rather than unexpected in view of the prior art. Since Piper clearly teaches that when glyburide is paired with metformin in a pharmaceutical formulation, the mass median particle size of glyburide is preferably 7-10 um (pg. 27, line 28) and that pioglitazone hydrochloride instead of glyburide can be paired with metformin as an antidiabetic agent (pg. 15, line 20), an artisan of ordinary skill would be motivated to use pioglitazone in the claimed particle size range (i.e., 7-10 um) and arrive at the instantly claimed invention. Therefore, applicant's alleged unexpected bioequivalence of pioglitazone would be an obvious expected result of the suggested formulation in Piper. It is noted that the instant claims are directed to a composition and according to MPEP 2112.02, products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or

claims are necessarily present as *In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)*.

Although Piper suggests that the mass median particle size of glyburide is preferably 7-10 um because this particle size assures reproducibility of glyburide dissolution and bioavailability from a metformin hydrochloride-glyburide tablet and not bioequivalence of a metformin hydrochloride-glyburide to Micronase (glyburide alone) as evidenced by Exhibit A, it is noted that the prior art's motivation to use pioglitazone in the instantly claimed particle size need not be the same as applicant's motivation. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Regarding the Declaration's results which show that the micronization of the pioglitazone particles did not significantly affect the uniformity of either of the active ingredients, it is noted that the examiner only used the teachings of Zhuang as motivation to have a similar biguanide median size to glyburide or its functional equivalent, pioglitzaone, resulting in a 1:1 ratio. The examiner did not suggest that an artisan of ordinary skill would have micronized pioglitazone for the purpose of increasing uniformity, as stated in applicant's arguments on pg. 6, first paragraph. Furthermore, it is not clear in Table DD4 of the Declaration what the particle size of metformin is compared to pioglitazone or even how different the micronized pigolitazone is from the non-micronized pioglitazone in size. Therefore, given applicant's incorrect assumptions,

mere arguments, and missing information, the examiner disagrees with applicant's conclusion that such results are opposite to the examiner's conclusion.

Absent any persuasive unexpected results, it is the position of the examiner that the rejections should be maintained for the reasons stated above.

Conclusion

Claims 15-17 and 19-25 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/David J Blanchard/
Primary Examiner, Art Unit 1643